Attach to #11

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

BARNETT et al.

Serial No.: 09/610,313 Art Unit: 1633

Filing Date: July 5, 2000 Examiner: B. Whiteman

Title: POLYNUCLEOTIDES ENCODING ANTIGENIC HIV TYPE C POLYPEPTIDE, POLYPEPTIDES AND USES THEREOF

6/13/02 DTN Considered

DECLARATION OF SUSAN E. WILSON, Ph.D.

PURSUANT TO 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Susan E. Wilson, hereby declare as follows:

1. I received my Bachelors of Science Degree in Pharmacology from the University of Leeds, United Kingdom in 1984; a Masters of Science Degree in Immunology from King's College, University of London, United Kingdom in 1988 and a Doctorate of Philosophy Degree in Immunology and Virology in 1999 from St.

Bartholomew's and the Royal London School of Medicine & Dentistry, University of London, UK.

2. I am currently Associate Director of Protein Therapeutics at Chiron Corporation and have held this position since September, 2000. Before joining Chiron, I worked in research relating to HIV. Additional details regarding my background and qualifications can be found in the accompanying copy of my *Curriculum Vitae*.

3. I have reviewed pending Patent Application Serial No. 09/610,313 for "POLYNUCLEOTIDES ENCODING ANTIGENIC HIV TYPE C POLYPEPTIDE, POLYPEPTIDES AND USES THEREOF" by Barnett, et al., (hereinafter "the specification") including pending claim 4. I have also reviewed the Office Action dated September 21, 2001. Therefore, I am familiar with the issues raised by the Examiner in the Office Action.

4. I understand that claim 4 is directed to an expression cassette, comprising multiple polypeptide-encoding nucleotide sequences. At least one of these polynucleotide sequences encodes a polypeptide including an HIV *Pol* polypeptide having at least 90% identity to the sequence of SEQ ID NO:30, 31 or 32. It is further my understanding that, in addition the *Pol*-encoding sequence(s), the expression cassette also carries one or more cytokine-encoding polynucleotides.

5. In July of 2000, when the specification was filed, a typical scientist working the field of cytokines had a Ph.D. in the Biological or Chemical Sciences and two to five years of relevant experience. I will call such a person a "typical scientist."

6. When the specification was filed, it clearly conveyed to a typical scientist that the inventors had in their possession the invention of claim 4 (as set forth in paragraph 4, above). By "in their possession," I mean that the inventors contemplated the expression cassette as set forth in claim 4 and that they had, using the specification and information available to a typical scientist, a practical way of making such an expression

cassette. Thus, I believe that a typical scientist would have understood the specification clearly described all of the various aspects of claim 4. I base this belief on the facts set forth below.

7. First, at the time the specification was filed, it was widely known how to construct expression cassettes, including expression vectors having two or more polypeptide-encoding sequences. Such methods are described in detail in the specification, for example, in Section 2.2.3 of the specification. Therefore, it is my opinion that construction of an expression cassette as set forth in claim 4 would have been routine to a typical scientist working in this area in view of the teachings of the specification.

8. Second, it would have been clear to a typical scientist that the inventors had in their possession the various polynucleotide components of the expression cassette of claim 4. HIV *Pol*-encoding sequences (SEQ ID NOs:30, 31 and 32) were clearly set forth in the Figures 8, 9 and 10 at the time of filing. Additionally, the specification clearly describes how to determine those sequences having 90% sequence identity to the claimed HIV *Pol*-encoding sequences of SEQ ID NOs:30, 31 and 32. (See, for example page 19, line 19 to page 22, which describes the use of available programs for calculating identity or similarity between sequences). Details and examples of how to determine sequence identity are also provided. (See, e.g., page 20, lines 1-7 and 14-25 and page 75, lines 29-33). Thus, it is my opinion that the HIV *Pol*-encoding sequences of the expression cassette of claim 4 are fully described in the specification.

9. Third, at the time the specification was filed, it would have been clear to a typical scientist that the inventors' specification fully described and contemplated an expression cassette that included both HIV *Pol*-encoding polypeptides as set forth above in paragraph 5 and one or more additional cytokine-encoding polynucleotides. Both cytokines themselves and polynucleotides encoding these cytokines were widely known

at the time of filing and were disclosed in the specification as filed. (See, *e.g.*, Section 2.2.1.5 starting on page 37 of the specification; and Section 2.3.2 staring on page 49 of the specification). Such cytokines were also commercially or publically available, as were polynucleotide sequences encoding these cytokines. (See, *e.g.*, page 37, lines 21-29 of the specification). Taken as whole, the specification unambiguously conveyed to a typical scientist that the inventors contemplated including a polynucleotide encoding one or more cytokines in expression cassettes comprising the HIV *Pol*-encoding sequences disclosed in the specification. In sum, based on the disclosure of the specification and the level of knowledge of a typical scientist regarding cytokines and expression cassettes at the time of filing, I believe that the specification as filed clearly conveys that the applicants had invented the expression cassettes as set forth in claim 4.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

3-19-02
Date

Susan E. Wilson Ph.D
Susan E. Wilson, Ph.D.

CURRICULUM VITAE

Susan Elizabeth WILSON
1600, High Street
Alameda, CA 94501

Tel (Hm): (510) 865-2116
Tel (Wk): (510) 923-8142
E-mail: susan_wilson@chiron.com

Employment History

09/00-present **Associate Director, Protein Therapeutics**
Chiron Corporation, Emeryville, CA 94608

- ➢ Research and Preclinical Development Project leader Chiron IL-2 Mutein Program
- • Management of multidisciplinary team including internal/external protein expression technologies and purification, Immunology and Pharmacology
- • Development of in vitro immunoassay systems including human NK cell-based moderate-throughput immunoassays (proliferation, cytotoxicity (NK/LAK/ADCC), cytokine production, cell survival)
- • Development/application of preclinical *in vivo* syngeneic solid and metastatic tumor (melanoma, colon carcinoma, breast cancer) and xenogenic (lymphoma and breast cancer) murine models for preclinical IL-2/cancer antibodies studies
- ➢ Preclinical Representative for IL-2 Oncology (Proleukin, Proleukin/anti-cancer antibody combinations) and IL-2 HIV core teams
- • Development strategy for Proleukin and next generation IL-2 related products
- • Regulatory responsibilities (IB updates, IND, BLA)
- • Scientific lead for IL-2 HIV regulatory strategy (presentations to US and European Clinical and Scientific Expert panels, AFFSAPS, EMEA, FDA)
- ➢ Clinical protocol Immunologist
- • IL-2 Oncology Phase I/II (IL-2 in combination with Rituxan, IL-2 in combination with Herceptin
- • IL-2 HIV Phase III (SILCAAT) clinical program
- • Scientific oversight and collaboration management of 19 immunology laboratories (USA, Canada, Australia and France) supporting SILCAAT IL2/HIV Phase III trial
- • Scientific selection, oversight and collaboration management with immunology laboratories supporting Phase I/II IL-2 Rituxan and Phase I/II IL-2 Herceptin studies
- ➢ Established/direct in-house immunology laboratory facility specializing in immunological assays in support of IL-2/Therapeutic Antibody Oncology Phase I-II clinical trials
- • NK/LAK/ADCC cytotoxicity assays & flow cytometric immunoassays
- ➢ Scientific review
- • Novel immunotherapeutic in-licensing and out-licensing opportunities/related IP

2/00-08/00 **Senior Staff Scientist, Adult Oncology**
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115

- ➢ Recruited to establish an immunology clinical endpoints laboratory to support translational clinical research and Phase I clinical trials of novel immunotherapeutic approaches to the treatment of cancer
- ➢ Design and optimization of state-of the art cellular techniques to evaluate novel anergization protocols utilizing CTLA-4, anti-B7.1 and B7.2 humanized mAbs in stem cell transplantation

- Project management duties include establishing interface between clinical endpoints laboratory and clinical staff, cell processing and stem cell/transplantation laboratories, industrial partners and associated collaborative research groups

5/96-2/00 **Senior Research Scientist, HIVNET Central Laboratory**
State of California Department of Health Services, Berkeley, CA 94704

- Established cellular immunology laboratory in accordance with GLP standards
- Specializing in functional cytotoxic and proliferative T-lymphocyte based immunoassays providing support for Phase I-III clinical trials of candidate HIV-1 vaccines
- ^{51}Cr release assays, antigen-specific IFN-γ ELISPOT & intracellular cytokine (IL-2, IL-4, IFN-γ) and chemokine (RANTES, MIP-1α and MIP-1β) flow cytometric analysis (IC FACS), proliferation assays and viral suppression assays
- Transfer of relevant scientific technology including:
  - Extensive tissue culture including adherent and non-adherent cell lines
  - EBV-transformation and expansion of B-lymphoblastoid cell lines
  - QC/QA production of recombinant vaccinia vectors expressing HIV-1gene(s),
  - QC env gp120, gp41, gag p24, pol and nef gene specificity screening by PCR,
  - HIV-1 gene product expression by immunoperoxidase and IC FACS,
  - DNA isolation and outsourcing HLA class I and II molecular typing,
- Responsible for recruitment, training and supervision of multi-disciplinary scientific team
- Project management activities included regular interface between HIVENT CTL laboratory, NIH DAIDS, clinical sites and statistical center, scientific data analysis and reporting, design and implementation of related ancillary studies
- Co-investigator/collaborator on NIH/NIAID sponsored HIV-1 research and clinical programs in US, Africa (Uganda and South Africa), S. America (Brazil) and Caribbean (Haiti and Trinidad)
- Preceptor UC Berkeley MPH Infectious Diseases Program
- Collaborative research projects:
- Analysis if cross-clade HIV-1 specific CTL reactivity and HLA genetic background in diverse ethnic populations (US, South Africa, Zambia, Brazil)
- Characterization of human CD8+ T-lymphocyte subpopulations: Relationship between phenotype, cytokine and chemokine production and naïve, memory or effector cell function

5/94-4/96 **Research Fellow for Peptech (UK), Academic Virology and Medical Microbiology**
St Bartholomew's & the Royal London School of Medicine & Dentistry, UK

- Investigate role of HIV-1 encoded mimics of alloantigens and immunopathogenesis of HIV-1 infection
- Responsible for transfer of relevant scientific technology from HIVER Ltd. to Peptech UK
- Established immunology laboratory investigating role of small synthetic peptides and modulation of TNF-α induced viral replication
- Supervised internal B.Sc students and external M.Sc student interns from London School of Hygiene and Tropical Medicine

1992-1994 **Research Fellow for HIVER Ltd. (UK) Dept. Immunology**
University College London, London, UK

- Investigate role of HIV-1 encoded mimics of self-antigens in immunopathogenesis of HIV-1 infection
- HLA typing by serology and molecular probes, proliferation and CTL assays, CD4+ and CD8+ T-cell cloning and characterization of putative pathogenic epitope(s)
- Provided collaborative support for Dept. Rheumatology (UCL) and T-cell responses in SLE patients
- Presentation of data to funding organization and internal/external scientific meetings

1989-1992 **Research Associate (1B), Dept. Microbiology**
St. George's Hospital Medical School, London, UK

- Established and maintained P3 HIV-1 research laboratory
- Research studies focussed on characterizing HIV-1 Gag p24 specific T-cell responses in humans and mice
- Analysis and presentation of research data at UK MRC and relevant scientific meetings

1988-1989 **Research Associate (1B), Dept. Medicine**
King's College Hospital Medical School, London, UK

- Characterized T cell responses in murine models of autoimmune thyroiditis

1985-1988 **Research Pharmacologist, Dept. Anti-Inflammatory Disease**
Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK

- Member of a team engaged in screening putative anti-inflammatory compounds in animal models of type II collagen and adjuvant-induced arthritis
- Elucidation of mechanism of action of novel immunosuppressive compounds
- Ex vivo studies of T-cell chemotaxis induced by stimulation of the CD4 receptor
- Modulation of mitogen, alloantigen and antigen-specific CD4+ T-cell responses by novel immunotherapeutic compounds
- Analysis of research findings and presentation at in-house R&D meetings

1984-1985 **Staff Toxicologist, Life Science Research Ltd., Suffolk, UK**

- Design and implement toxicology/oncology studies in small animals
- Experience in compilation of SOPs, animal husbandry, drug formulation, necropsy, histology and pathology, data collation and analysis, internal QC and auditing, drafting and editing final reports for clients

EDUCATION

1984 B.Sc (Honors) Pharmacology, University of Leeds, UK

1986-1988 M.Sc Immunology, King's College, University of London, UK
Thesis: Leukocyte Migration in Response to Stimulation of the CD4 Molecule

1994-1998 Ph.D Immunology and Virology (conferred 1999)
St. Bartholomew's and the Royal London School of Medicine & Dentistry,
University of London, UK
Thesis: The Role of CD8+ T-lymphocyte Mediated Immunity in HIV-1 Infection.

SOCIETY MEMBERSHIP

British Society for Immunology (1986-present)
British Antibody Club (1986-present)

PUBLICATIONS

Bloxham D.P., Bradshaw D., Dodge B.B., and **Wilson S.E.** (1986). Role of Interleukin-1 on the effects of retinoids in 'non-responder' collagen arthritic rats. *Brit. J. Pharmac.* **89:** 817.

Bradshaw D., Dodge B.B., Franz P.H., Lewis E.J., and **Wilson S.E.** (1986). Comparative effects of Tenoxicam on type II collagen arthritis in the rat. *Brit. J. Pharmac.* **89:** 826.

Wilson S.E. Hawkes J.E., Bradshaw D., and Westmacott D. (1988). The effect of sulphasalazine and its metabolites on collagen arthritis in the mouse. *Brit. J. Pharmac.* **90:** 515.

Wilson S.E., Hallakova E., Mascagni P., Gibbons W. and Coates A.R.M. (1991). Further characterization of the proliferative response to HIV-1 Gag p24 in HIV seronegative and asymptomatic HIV seropositive donors. *Modern Approaches To New Vaccines Including Prevention of AIDS.* Cold Spring Harbor Laboratory., New York, USA. pp. 74.

Dalgleish A.G., **Wilson S.E.,** Gompels M., Ludlam C., Gazzard B., Coates A.R.M. and Habeshaw J.A. (1992). T-cell receptor variable gene products and early HIV-1 infection. *Lancet.* **339:** 824.

Wilson S.E. and Aston R. (1994). Recent developments in macrolide immunosuppressants. *Exp. Opin. Ther. Patents.* **4:** 1445-1459.

Wilson S.E., Habeshaw J.A. and Oxford J.S. (1996). Modeling HIV concentration during acute AIDS infection. *Science.* **272:** 1960-1961.

Wilson S.E., Hounsell E.F., Addawe M., Oxford J.S. and Habeshaw J.A. (1997). HIV-1 gp120 C-terminal peptide induced human CD8+ T cells lines suppress heterogeneous antigen-specific self-MHC class II-restricted CD4+ T-cell responses. *AIDS. Res. Human Retroviruses.* **13:** 1313-1324.

Wilson S.E., Pedersen S.L., Kunich J.C., Wilkins V.L., Mann D.L., Mazzara G.P., Tartaglia J., Celum C.L., and Sheppard H.W. (1998). Cross-clade envelope glycoprotein 160-specific CD8+ cytotoxic T lymphocyte responses in early HIV type 1 clade B infection. ***AIDS Res Hum Retroviruses* 14:** 925-937

Habeshaw J.A., **Wilson S.E.,** Hounsell E.F., and Oxford J.S. (1999). How HIV-1 lentivirus causes immune deficiency disease. ***Med Hypotheses*** 52:59-67

Wilson S.E., Kunich J.C., Mann D.L., Pedersen S.L., Mazzara G.P., Celum C.L., and Sheppard H.W. (2000). Cross-clade Gag p55, Pol and Nef specific CD8+ cytotoxic T lymphocyte responses in early HIV type 1 clade B infection. *AIDS Res Hum Retroviruses.* Submitted for publication.

Wilson S.E., Kunich J.C., Lee C.W., Schreiber K., Propst M. and Sheppard H.W. (1999). Single cell analysis of cytokine and beta chemokine production by T cells from HIV-1 infected individuals: Relationship to CD4 and CD8 phenotype. *J. Immunol.* In preparation.

Oral Presentations

Wilson S.E., Hallakova E., Mascagni P., Gibbons W. and Coates A.R.M. (1990). Characterization of the proliferative response to HIV-1 gag p24 in HIV seronegative and asymptomatic HIV seropostive donors. MRC ADP. Exeter, U.K.

Wilson S.E. (1990). Human T cell responses to HIV-1 gag p24. Microbial Antigens in Immunoregulation. The Antibody Club. London, U.K.

Wilson S.E., Gompels M., Ludlam C., Gazzard B., Coates A.R.M. and Habeshaw J.A. and Dalgleish A.G., (1992). HIV- infection and development of autoimmunity. Analysis of TCR repertoire in early HIV-1 infection. Int. Conf. Cell. Mol. Aspects of Self-reactivity and Autoimmune Disorders. Taormina, Sicily. Abstr. 78.

Wilson S.E. (1992). Immunological Mechanisms in the Rheumatic Diseases. The role of MHC and TCR genes in disease. Current Concepts in Rheumatology. St. George's Hospital Medical School, University of London, London, U.K.

Wilson S.E., Gompels M., Ludlam C., Gazzard B., Coates A.R.M. and Habeshaw J.A. and Dalgleish A.G., (1992). Positive selection of the V□ 5 TCR gene products in HIV-1 infected individuals. VIIIth Int. Conf. AIDS, Amsterdam Netherlands. Oral Comm. ThA 1537.

Wilson S.E. (1994) HIV-1 envelope gp120 encoded MHC mimicry and loss of immune regulation. Seminar series. Dept. Immunology. Royal Postgraduate Medical School. Commonwealth Building, Hammersmith Hospital, London, U.K.

Wilson S.E. and Habeshaw J.A. (1995). The role of HIV-1 encoded MHC mimicry in HIV-1 immunopathogenesis. MS3. Evasion and subversion of the immune system. Third Annual Congress Joint Meeting with the NVVI. 6-8th December 1995. Brighton Conference Center, Brighton, Sussex, U.K.

Addawe M.D., Fabrizzi F., Dourmashkin R., **Wilson S.E.** and Oxford J.S. (1996) Chemically inactivated whole HIV vaccine induces cellular responses in mice. Vancouver. XI International Conference on AIDS. Mo. A. 100.

Wilson S.E. (1997) CTL responses in HIV Infected and Vaccinated Subjects: Similarities and Differences. Invited speaker at Seminar on HIV Vaccines – Humoral and Cellular Immunity sponsored by Henry M. Jackson Foundation and Walter Reed Army Institute of Research, Rockville, M.D., USA. Chiang Mai, Thailand. October 20-22, 1997.

Wilson S.E., Pedersen S., Kunich J.C., Mazzara G., Tartaglia J., Mann D., Celum C., and Sheppard H.W. (1998). Cross-clade envelope gp160, Gag p55 and Pol Specific CD8+ CTL Responses Early Following HIV-1 Clade B Infection. 12th World AIDS Conference, Geneva, Switzerland. June 28-July 1998.

Wilson S.E. (1999). The role of CD8+ CTL responses in HIV-1 Infection. Comparison of cross-clade Env gp160, Gag p55 and Pol Specific CD8+ CTL responses in natural HIV-1 clade B infection versus HIV-1 clade B based vaccine recipients. National Institute of Virology, Johannesburg, South Africa, December 7TH 1999.

Wilson S.E. (2000). The Role of IL-2 in T-cell Homeostasis. T-cell Dynamics in HIV Infection: Implications for Immune-Based Therapies. Satellite Symposium 41st ICAAC, Chicago IL, Dec 15, 2001.

Poster Presentations

Wilson S.E., Hallakova E., Mascagni P., Gibbons W. and Coates A.R.M. (1991). Further characterization of human proliferative T cell responses to HIV-1 gag p24 in HIV-1 seronegative and asymptomatic seropositive donors. . British Society of Immunology Spring Meeting, London, U.K. Abst. 3.15.

Wilson S.E., Hallakova E., Mascagni P., Gibbons W. and Coates A.R.M. (1991). Identification of T cell epitopes of HIV-1 gag p24 recognized by asymptomatic HIV seropositive and control individuals from low-risk groups. VIIth Int. Conf. AIDS. Florence, Italy, W.A. 1208.

Wilson S.E., Hounsell E.F. and Habeshaw J.A. (1993). Generation of auto- and allo-cytotoxic T cell responses by regions of HIV-1 gp120/41 which share sequence homology with human MHC Class I/II. Ixth Int. Conf. AIDS, Berlin, Germany. PO-A19-0373.

Wilson S.E., Hounsell E.F. and Habeshaw J.A. (1993). The role of molecular mimics of human self-antigens encoded within HIV-1 gp120 in the immunopathogenesis of HIV disease. Abstr. 135. MRC ADP, Brighton, U.K.

Wilson S.E., Addawe M., Hounsell E.F., Oxford J.S and Habeshaw J. A. (1996). HIV-1 gp120 C-terminal peptide induced human CD8+ T cells lines suppress heterogeneous antigen-specific self-MHC class II-restricted CD4+ T-cell responses. British Society for Immunology, Bristol., UK.

Celum C.L., **Sheppard H.W.,** Donnell D., Wilson S.E., Douglas J., Mayer K., Flores J., Marmor M. and Buchbinder S.P. (1997). HIV seroconverters in the HIVNET: Clinical, epidemiologic, virologic, and immunologic findings in primary HIV infection. National Conference on HIV-1 Vaccine Design Goals, NIH, Bethesda, MD, USA.

Wilson S.E., Kunich J.C., Lee C.-W., Schreiber K., Propst M. and Sheppard H.W. (2000). Single cell analysis of cytokine (IL-2, IL-4, IFN-g) and beta chemokine (MIP-1a, MIP-1b, RANTES) production by CD4+ (CD8-) and CD8+ T-lymphocytes from HIV-1 infected long-term nonprogressors and progressors. 7^{ih} Conf. Retroviruses and Opportunistic Infections, San Francisco, CA. Jan 31- Feb 2, 2000.

Wilson S.E., Hurst D., Yuen A., Gluck L., Dayton M., Gockerman J., Levine A., Navis D,, Zhou L., DiFrancesco A,, Milan S., Wolin M. (2001) IL-2 Mediated NK Cell Expansion Correlates with Clinical Response to Rituximab: Results of Two Phase I Trials of the Combination of IL-2 and Rituximab. 43rd Annual Meeting, American Society Hematology, Orlando, FL. Dec 7-11, 2001. Blood. 98: 11: Part 1 Poster 2525.

Hurst D., Gluck L., Yuen A., Levine A, Dayton M., Gockerman J.P., Lucas J., Denis-Mize K., DiFrancesco A., Navis D., Samara E., Tong B., Milan S., **Wilson S.E,,** and Wolin M. IL-2 plus Rituximab results in clinical responses in advanced patients with non-Hodgkin's lymphoma related to the degree of NK expansion. Accepted for 38th Annual Meeting of American Society for Clinical Oncology, Orlando, FL May 18-21, 2002.